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DESIGN, DEVELOPMENT AND EVALUATION OF DOMPERIDONE PELLETS

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Running Title: Dissolution enhancement of Domperidone Pellets

ABSTRACT: Gastroesophageal reflux is very common in youth. If conservative procedures fail to relieve it, the use of a potent antiemetic agent that facilitates gastric motility and emptying, such as Domperidone, is vindicated. Domperidone is a synthetic benzimidazole compound that acts as a dopamine D2 receptor antagonist. Its localization outside the blood-brain barrier and antiemetic properties has made it a useful adjunct in therapy for Parkinson's disease. There has been rehabilitated curiosity in antidopaminergic prokinetic agents since the abandonment of cisapride, a 5-HT4 agonist, from the market. Domperidone is also as a prokinetic negotiator for treatment of upper gastrointestinal motility disorders. It continues to be an attractive alternative to metoclopramide because it has fewer neurological side effects. Patients receiving Domperidone or other prokinetic agents for diabetic gastropathy or gastroparesis should also be managing diet, lifestyle, and other medications to optimize gastric motility. The aim of the investigation is to improve the dissolution behavior of Domperidone, a dopamine antagonist. Extrusion–spheronization technique, a possible approach for ensuring maximum dissolution and uniform pellet size almost spherical so as to achieve the smooth gastric transit of drug have been estimated. Pellets were prepared utilizing Extrusion–spheronization technique and all the process parameters such as excipient ratio, stirring speed, temperature, and effect of aggregating agent on the pellets formulation have been optimized. The addition of an aggregating agent (isopropyl alcohol) improved the uniform pellets formation and the method was reproducible. Formulated pellets showed clear and highly improved *in vitro* dissolution behavior, probably due to Critical micelles concentration of surfactant (Sodium Lauryl Sulfate). The pellets drug was stable at room temperature, 25°C/60% RH, 30°C/65% RH and 40°C/75% RH as per ICH guidelines, after 3 months.

Key Words: Pellets, Extrusion–Spheronization, Domperidone, Sodium Lauryl Sulfate.

INTRODUCTION

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their appropriateness for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules. Pellets are gradually more being used as multiple unit dosage form. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

Pelletization involves the process of renovation of fine powder or granules of bulk drugs and the excipients into small, free flowing, spherical units in size between 0.5-1.5 mm, referred to as pellets (figure 1). Fabrication of pellets involves use of extruder and spheronizer[1]. Assorted types of extrudates have common feature of forcing the extrudats from a wide cross-section through the restriction of the die[2]. The force required and the depiction of extrudats produced is dependent on rheological properties, the design of the die[1]. In spheronizers, a plate (diameter 10-1000 cm) rotates within the confines of a cylinder. The extruded, cylindrically shaped particles are broken into uniform length almost instantaneously and are gradually transformed into spherical shapes. A sphere has several geometric advantages over other forms such as lowest surface-to-volume ratio and because of its shape it is the earliest to coat[1].

The focal intent of the present cram was to develop and portray a extrusion-spheronization process for preparing sucrose beads and subsequent Domperidone drug layered pellets and study the effect of the sodium lauryl sulfate release rate profile of Domperidone pellets.

MATERIALS AND METHODS

MATERIALS

Domperidone was obtained as gift sample from Micro Labs Bangalore, Starch from S.B Inpex, Povidone from I.S.P Technologic Inc Texascity. Micro Crystalline Cellulose from Powder Rant Renidice Pvt. Ltd, Quinollin Yellow from Rohadyc Chem Pvt. Ltd, Sodium Lauryl Sulfate from Bendale Chemicals, Iso-propyl Alcohol from Deepak Fertilizers and Petrocam Ltd. All other ingredients used were of analytical grade.

METHODS

Preparation of pellets

Extruder-spheronizer technique was used for preparation pellets. Pelletization techniques were optimized with respect to the proportion of diluents, spheronization speed, spheronization residence time (dwell time) and concentration of surfactant (table 1). Pellets were prepared using Domperidone with microcrystalline cellulose, starch as diluents, povidone and Iso-propyl alcohol solution as binder. The material previously passed through 80 # was mixed thoroughly and kneaded using povidone solution quantity sufficient to obtain mass of right consistency. Extrudates collected into the tray were spheroinized at optimized speed of 1400 rpm for 4-6 minutes this treatment led to the formation of multiple layers of drug particle around and non pareil seed resulting in the production of pellets and were dried at 40ºC for 3 hours in tray dryer[1]. Dry pellets were passed through 16 # and fraction retained on 32 # was collected for auxiliary characterization.

Evaluation of powder blend and pellets

The formulated powder blend were evaluated for compatibility, particle size shape analysis using Malvern particlesizer (MS 2000)[3], angle repose[4], hausner's ratio, compressibility index, bulk density, true density and Granule density[3].

In-vitro Dissolution studies

The release of drug from the developed formulations in the environment of gastrointestinal tract was determined using the USP XXIII dissolution apparatus II (Electro lab TDT – 08L). Capsules containing pellets in beaker containing 900 ml of dissolution media maintained at 37 ± 0.5°C and 100 rpm. For cumulative release studies, dissolution media consisted of buffer solution of 0.1 HCl for one hour. Aliquot samples of 10 ml were withdrawn every 5 minutes each time with the same amount of fresh medium. Correction factors for each aliquot were considered in calculation of release profile. Absorbance of sample after proper dilution was measured at 285 nm using U.V. spectrophotometer (Shimadzu) against blank. Concentration of drug was determined from the standard plots of the drug in buffer (figure 2) and the percentage drug release was calculated at each sampling time.

Accelerated stability studies

Formulation were stored at various temperature *viz.*25°C/60% RH, 30°C/65% RH and 40°C/75% RH as per ICH guidelines and various physicochemical parameter (appearance, percentage drug content and release profile) were monitored periodically for 3 months.

RESULTS AND DISCUSSION

Domperidone pellets formulated, by using different concentration of surfactant like sodium lauryl sulfate. Domperidone which is preferably used as a dopamine receptor blocking for chemo emetic trigger zone. Pellets were prepared by applying extruder-spheronizer technique. Domperidone meets all the ideal characteristics to formulate in the form of oral drug delivery system.

Under Preformulation study, FTIR analysis between the drug and enteric polymer mixture showed no unaccountable extra peaks, which confirms the absence of chemical interaction between the drug and polymer.

Physical characterization

Powder blend of Domperidone and pellets were evaluated for various physiochemical parameters. The organoleptic properties were complied with the British Pharmacopeia specification. Physical properties such as particle size analysis, bulk density of raw material powder, Melting point. Moisture content determination using Karl Fisher titration gave the information about purity of the drug powder respectively. Solution properties solubility evaluated, results were complied with the pharmacopeia specification. Loss on drying was within the British Pharmacopeia limit and the result of angle of repose of powder showed the poor flow properties. Angle of repose and flow rates of the different formulations was observed when compared with bulk drug of Domperidone. That shows after pellets formulation excellent flow properties and flow rate also excellent. Assay of Domperidone was carried out by titration method was found to be 99.7% (99 – 101%). Technological characterization of formulated Domperidone powder blend and pellets formulation are shown in table 2.

Drug Content:

Samples were analyzed spectrophotometrically by SHIMADZU UV 1700 UV-Vis Double beam spectrophotometer at a wavelength of 285nm. Equivalent weight to 25mg of Domperidone pellets was dissolved with methanol and, 5ml aliquot of this solution admix with 50ml of 0.1N HCl, the drug concentration in the HCl phase was determined by proper dilution.

In Vitro Dissolution Studies

The dissolution rate studies for each of the formulations were performed in order to assess the effect of increase in surfactant concentration on release profile. In dissolution studies, 900ml solution of 0.1N HCl was taken for one hour to mimic the cumulative release of drug in stomach. Result of *in vitro* dissolution rate studies are shown in table No 4 and figure 3 and regression analysis in table 2 Release pattern of all the formulation was determined and mechanism of release was predicted based on higuchi plot.

***Drug release kinetics*[5]**

Kinetics studies were done which shows that F2 follows Higuchi plot which deals that drug release by diffusion.

Accelerated stability studies

The selected formulations were subjected for accelerated stability studies as per the ICH guidelines. There were no changes in appearances and percentage drug content of pellets stored at different temperature for drug remaining *vs.* time at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH. All the parameter was within the limit after 90 days.

CONCLUSION

Based on the *in vitro* data's formulation no F7 was found to have selective drug release pattern among the formulation prepared containing 0.06% sodium lauryl sulfate yielded desired drug release within 45 minutes. This definitely improves patient's compliances and reduces the gastric side effect.

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Table 1: ***Optimization of process parameters for pelletization technique***

Parameter	Batch no.	Parametric value	Description of pellets obtained
Diluents : MCCP	F01A1	6:50	Rod shaped
	F01A2	8:48	Rod shaped and brittle
	F01A3	16:40	Spherical and brittle
	F01A4	10:46	Spherical and brittle
	F01A5	12:44	Spherical and Hard
Spheronization speed (rpm)	F01B1	100	Rod shaped
	F01B2	500	Dumble shaped
	F01B3	900	Spherical – sub spherical
	F01B4	1200	Spherical – sub spherical
	F01B5	1400	Spherical
Spheronization residence time (min)	F01C1	1	Rod shaped
	F01C2	2	Rod shaped
	F01C3	3	Rod shaped
	F01C4	4	Spherical
	F01C5	5	Spherical

Table 2: ***Technological characterization of formulated Domperidone powder blend and pellets formulation****

Parameters	Domperidone	F01	F02	F03	F04	F05	F06	F07
Angle of repose*	35.11± 0.561	16.23± 0.08	16.48± 0.14	16.06±1.36	16.93±0.15	16.18±0.63	16.14±0.04	16.52±0.06
Flow rate gm/sec*	-	1.58±0.13	1. 77±0.19	1.58±0.13	1.69±0.29	1.58±0.13	1.61±0.33	1.58±0.13
Hausner's ratio	-	1.05	1.04	1.06	1.05	1.04	1.06	1.04
Compressibility index (%)	-	16.8	16.6	16.9	16.8	16.6	16.9	16.6
Bulk density (gm/ml)*	0.55±0.02	0.78± 0.01	0.78± 0.01	0.76±0.03	0.78±0.01	0.78±0.01	0.76±0.03	0.78±0.01
Tapped density (gm/ml)*	0.417 ± 0.035	0.82±0.01	0.83±0.01	0.81±0.01	0.82±0.01	0.82±0.01	0.81±0.015	0.82±0.01
Granules density*	-	1.99±0.001	1.97±0.01	1.97±0.01	1.98±0.05	1.96±0.002	1.97±0.031	1.99±0.02
Shape	-	Spherical	Spherical	Spherical	Spherical	Spherical	Spherical	Spherical
Arithmetic mean diameter (μm)	-	0.86	0.81	0.76	0.79	0.84	0.87	0.85
Loss on drying (%)	0.26	2.27	2.04	1.86	2.42	2.25	2.36	1.93
Moisture content	1.8	1.9	1.85	1.88	1.8	1.9	1.87	1.82
Friability%	-	0.25	0.37	0.21	0.25	0.31	0.24	0.25
Assay (%)	99.97	99.68	99.25	99.18	100.56	99.68	98.5	99.5
Higuchi Model, r^2	-	0.9956	0.9971	0.9959	0.9845	0.9896	0.9963	0.9039

***All values are mean ± S.D. for n=3**

Table 3: ***Formulations of Domperidone Pellets***

INGREDIENTS	Pellets formulation (gm/kg)						
	F01	**F02**	**F03**	**F04**	**F05**	**F06**	**F07**
Domperidone	160	160	160	160	160	160	160
Povidone	60	60	60	60	60	60	60
Starch	60	60	60	60	60	60	60
Sodium Lauryl Sulfate	-	0.100	0.200	0.300	0.400	0.500	0.600
M.C.C.P	220	220	220	220	220	220	220
Quinoline Yellow	4	4	4	4	4	4	4
N.P.S	496	496	496	496	496	496	496
Isopropyle Alcohol	1000	1000	1000	1000	1000	1000	1000

Table 4: ***In vitro Release Profile of Percentage cumulative drug release from various formulations*** *****

Time in mint	F01	F02	F03	F04	F05	F06	F07
5	42.28±0.55	46.02±1.06	50.22±1.10	53.69±1.57	55.20±0.91	56.20±0.11	85.29±1.49
10	51.26±0.22	53.40±1.12	57.82±1.81	56.8±0.67	59.25±1.15	63.18±1.57	90.08±0.57
15	55.98±0.26	56.81±0.69	61.87±0.58	64.81±1.81	66.70±1.08	69.88±0.613	91.29±1.61
25	64.06±1.08	64.00±1.62	68.80±1.88	73.63±1.20	75.11±1.23	78.16±1.07	92.52±1.99
35	68.48±0.47	70.52±1.27	76.75±1.90	80.73±0.97	82.96±1.11	86.50±1.16	93.86±0.50
45	72.46±1.42	74.42±1.43	80.41±0.49	84.02±1.14	86.30±0.71	90.34±0.85	96.01±0.76

***All values are mean ± S.D. for n=3**

Figure 1: ***Extrusion-Spheronization process***

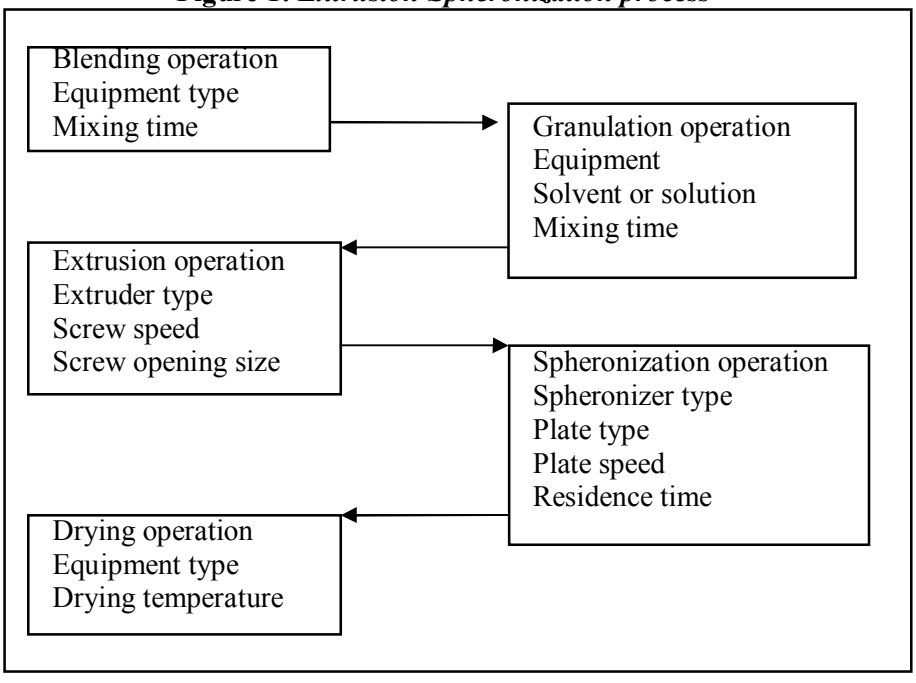


Figure 2: λ_{max} *for Domperidone in 0.1 N HCL*

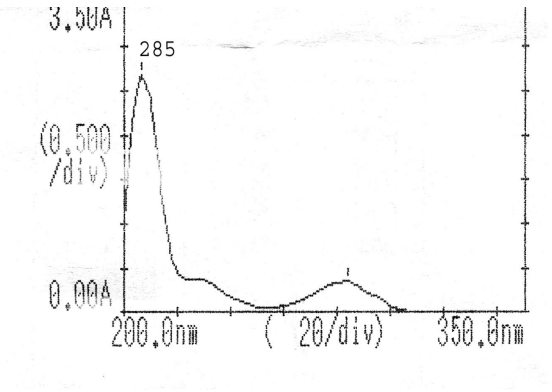


Figure 3: *Percent cumulative drug release for various formulations*

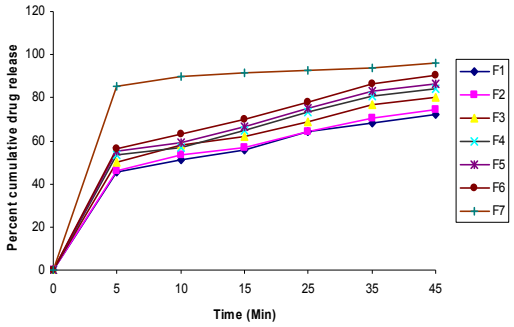


Figure 4: *HIGUCHI plot for F07*

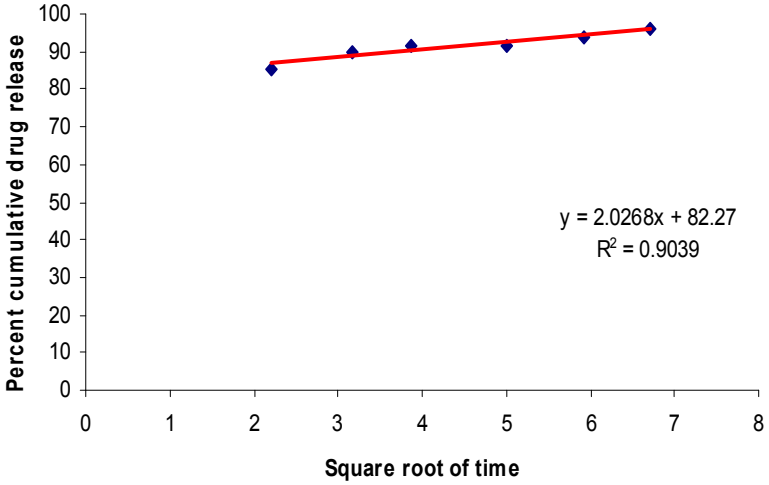


Figure 5: *FTIR spectrum of Domperidone*

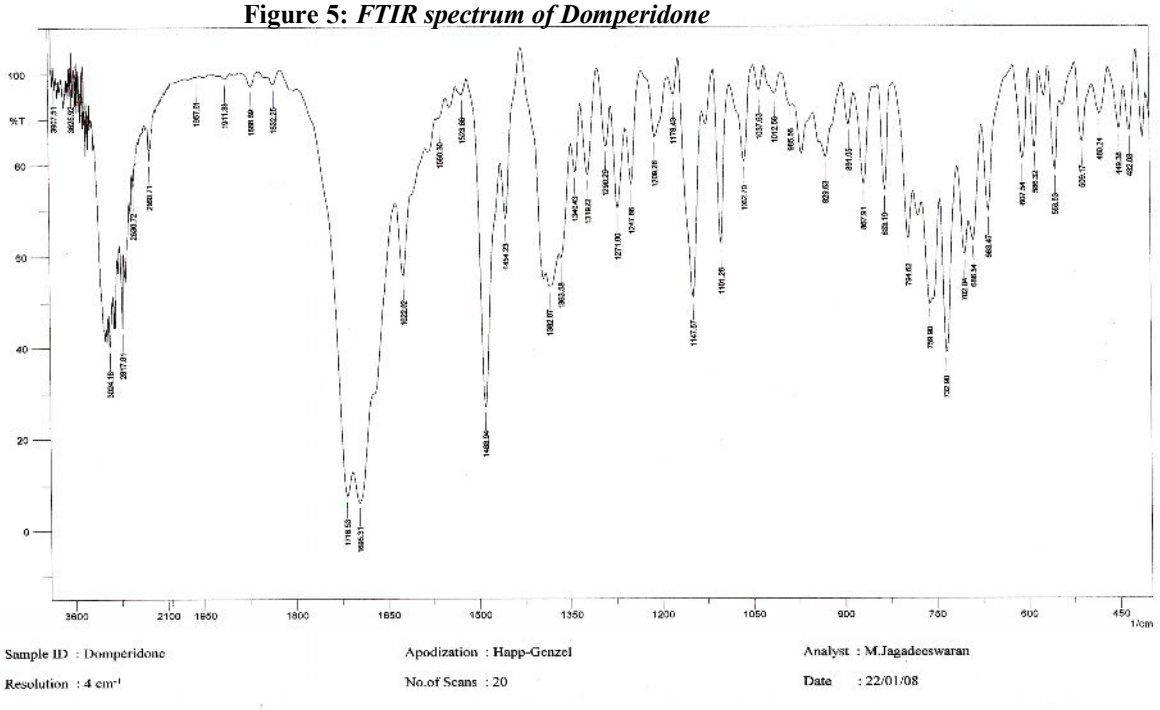
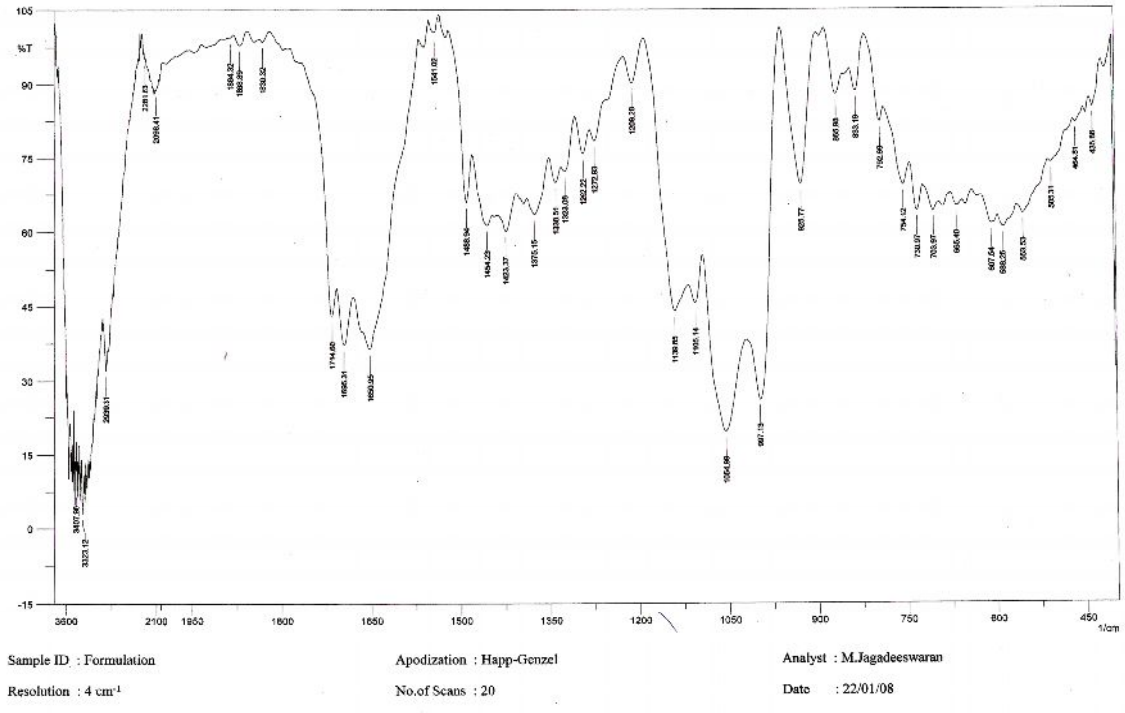


Figure 6: ***FTIR spectrum of physical mixture of drug and excipient***



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